REMARKS

Claims 1-112 were canceled without prejudice to Applicants' rights to pursue the subject matter in a subsequent patent application. Claims 113-119 were previously submitted in Applicants' response dated March 29, 2007. A copy of the March 29, 2007 Amendment is hereby attached as **Exhibit 1**, the contents of which are incorporated hereto by reference. There are no issues of new matters. Accordingly, applicants respectfully request the entry of this Amendment. Upon entry, claims 113-119 are now pending and under examination.

Examiner's comments are addressed in sequence below.

A. The Final Office Action Relies on Unsound Scientific Theory

When an Examiner relies on a scientific theory, evidentiary support for the existence and meaning of that theory must be provided. MPEP 2144.02, *citing In re Grose*, 137 USPQ 797 (CCPA 1963).

In the present case, Examiner makes a substantial assumption that is completely unsupported by any theory or evidence in the microbiological arts. Specifically Examiner assumes that the basis of the tumor-targeting phenotype can be reduced to a single, unitary "structure." There is no data on record or in the art to even suggest that this is the case. Therefore, basing the rejection on this unsound scientific "hypothesis" is improper and is insufficient to set forth a *prima facie* case of vague and indefinite claim language.

Further, the requirements for clarity and precision must be balanced with the limitations of the language and the science. If the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the statute (35 U.S.C. 112, second paragraph) demands no more. MPEP 2175.03 (Emphasis added).

C. "Toxic lipopolysaccharide (LPS)" is not Vague or Indefinite

Examiner asserts that "the amended claims recite "toxic LPS", and it is unclear what the structure of the toxic LPS is, and thus the metes and bounds of the claims are uncertain." Applicants respectfully submit that this rejection is improper and should be reversed.

Attention is respectfully directed to U.S. Patent Publication 20040229338, paragraphs [0152]-[0153]. These paragraphs describe that LPS is one of the bacterial substituents responsible for toxicity of bacteria. The text further indicates that persons of ordinary skill in the art may produce better tolerated bacteria, i.e., attenuated, by producing bacteria lacking toxic LPS. One way of achieving this is disruption of Lipid A synthesis.

Paragraphs [0152]-[0153] succinctly explain why it is indisputable that persons of ordinary skill in the art would have no problems appreciating that an attenuated bacterium that cannot produce toxic LPS will demonstrate an attenuated phenotype.

Applicants respectfully submit that the claim language would not be indefinite or vague to persons of ordinary skill in the art. As discussed above, Examiner substitutes her own state of

knowledge for those of ordinary skill in the art in order to maintain the rejections under § 112, 2nd paragraph.

In sum, the rejection of the claims under § 112, 2nd paragraph should be reversed. The rationale for the rejections is improper as it is not directed not toward understanding claim language, but requiring a nonexistent explanation of the invention's operability. Specifically, Examiner believes that a single structure confers the tumor-targeting phenotype and that it must be reflected in the claim. Similarly, Examiner's comments about the structure of "toxic LPS," are improper in view of the specification's explicit disclosure and knowledge of persons of ordinary skill in the art. Accordingly, reversal of the rejection is respectfully requested.

D. THE CLAIMED SUBJECT MATTER IS NOT OBVIOUS OVER THE COMBINATION OF LOW IN VIEW OF SCHACHTER

The pending claims are drawn to a method of inhibiting the growth or reducing the volume of a solid tumor by administering attenuated tumor-targeted bacteria and either cisplatin or cytoxan. In contrast, Schachter teaches using four distinct drugs (one of which is cisplatin) after treatment with IFN-α but before treatment with GM-CSF. Schachter, page 156, top col. 1, discussing the Del Prete reference. No tumor-targeting bacteria are disclosed.

ON PAGE 6 OF THE FINAL OFFICE ACTION, EXAMINER ASSERTS:

> The Office cited Schachter et al to show the need and motivation was present in the art to combine chemotherapy with bio-therapy, one could use either the cytokine biotherapy as taught by *Schachter et al,* or the attenuated *Salmonella* biotherapy as taught by *Low of* al with a reasonable expectation of success for treating cancer. It was within the levels of the skilled in the

art, and a matter of optimization to determine the proper dosing regimen so that the combined therapy would not lead to a detrimental effect.

Applicants respectfully disagree that a mere general reference to a "need and motivation" in the art, cannot provide a reasonable expectation of success. Further, said conclusion runs counter to current practice in the art. Accordingly, the combination of Low and Schachter does not provide a *prima facie* case of obviousness.

1. Proceeding contrary to accepted wisdom is evidence of nonobviousness. MPEP 2145(X.D.3). In contrast to Examiner's conclusion it is respectfully submitted that Appellants' use of tumor-targeted bacteria in a combination chemotherapy regimen goes against commonly accepted thinking in the chemotherapy arts. It is known that chemotherapy often results in a severe decrease of neutrophils, a condition known as neutropenia. A major result is a severely compromised ability of the cancer patient to fight infection against bacterial and fungal pathogens. *See* Freifeld, et al., (2004), *Fever in the Neutropenic Cancer Patient*, Chap. 46, Clinical Oncology, (3rd ed.), attached as **Exhibit 2**. It is known that when unopposed by innate neutrophil responses bacterial infections spread quickly and relentlessly.

Therefore, in contrast to Examiner's conclusion persons of ordinary skill in the art would be highly unlikely to employ Low's tumor-targeted bacteria in a chemotherapy regimen similar to that of Schachter. Accordingly, the combination of Low and Schachter are not sufficient to establish a *prima facie* case of obviousness and, therefore, the rejection should be reversed.

2. Examiner concludes, without any scientific explanation, that Low's tumor-targeted bacteria and Schacter's biotherapy regimen of two cytokines, IFN-α and GS-CSF, are freely interchangeable. Further, Low does not teach any combination therapy at all. Thus, the prior art does not provide any motivation or suggestion to combine the bacteria with only cisplatin or cytoxan. Examiner's rationale is nothing more than an obvious-to-try suggestion, which is not sufficient to make out a *prima facie* case of obviousness. In re Eli Lilly and Co., 14 USPQ 2d 1741, 1743 (Fed. Cir. 1990))(An "obvious to try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued.)

3. The rationale behind In re Kerkhoven is incorrectly applied in this case for two reasons. First, the technical subject in Kerkhoven is far more predictable than that in the present case. For example, in Kerkhoven mixing two detergent compositions to form a third effective detergent composition has a substantial expectation of success. This is known not to be the case with developing effective combination cancer therapies. The Office Action asserts that "one could use either the cytokine biotherapy as taught by Schachter et al, or the attenuated Salmonella biotherapy as taught by Low et al with a reasonable expectation of success for treating cancer." A major problem with this conclusion is that it does not take into consideration the unpredictability of effectiveness of combinations of chemotherapy agents.

Second, Examiner has not provided a single piece of evidence that tumor-targeted bacteria are ***art-recognized equivalents*** of IFN-α and/or GM-CSF. See MPEP 2144.06. Examiner loosely associates them under the umbrella of "biotherapy" in order to support her rationale. Respectfully, doing so has no art-recognized basis or any legal effect in establishing that they are art-recognized equivalents. Accordingly, it is respectfully requested that the rejection be reversed.

4. A comparison of the claimed method with the closest prior art available (i.e., Fig. 40) proves that the Examiner's allegation of a "reasonable expectation of success" is unfounded. Attention is respectfully directed to Figs 39 and 41, which show the supra-additive effect of the combination of bacteria and either cytoxan or cisplatin, respectively. In contrast, Fig. 40 demonstrates that the combination of mitomycin with the same bacteria provide no extra benefit over that provided by the bacteria themselves. Therefore, changing even one therapeutic agent may obliterate the supra-additive effect of the claimed method.

In view of this data, it cannot be reasonably concluded that combining Low and Schachter provides a reasonable expectation of success sufficient to make out a *prima facie* case of obviousness. Accordingly, the rejection should be reversed.

V. Conclusion

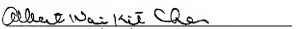
In sum, the rejection of the claims over Low/Schachter should be reversed. Examiner's proposed modification of Low is clearly contrary to current chemotherapy practice. Further, the remarks and experimental data show that persons of ordinary skill in the

art could not have had a reasonable expectation of success of combining the cited references and arriving at the claimed method. Further, Examiner's invoking the rule of Kerkhoven is misplaced and cannot support the instant rejection. Accordingly, the rejection under § 103(a) should be reversed.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-1891.

Respectfully submitted,



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